Substance Use Patterns and Cognitive Function in Patients with Methamphetamine Use: A Study of 131 Cases

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Objective: Substance use patterns are among many factors been reported to influence the result of cognitive function in patients with methamphetamine (meth) use. In this study, we intended to study what meth use parameters can predict cognitive deficits in patients with meth use. Methods: In this cross-sectional study, we recruited meth users, to collect meth use parameters—onset age, duration, dose, and experience of other illicit drugs. The psychiatric diagnoses, cognitive function, and clinical psychopathology of each patient were evaluated using the Diagnostic Interview for Genetic Study, the Brief Assessment of Cognition in Schizophrenia (BACS), and the Brief Psychiatric Rating Scale, respectively. Results: We enrolled 131 patients with meth use. After controlling for age, sex and education, we found that long duration of meth use and experience of ketamine use were significantly associated with poor performance in working memory (p < 0.01), executive function (p < 0.05) and composite BACS score (p < 0.01 and p < 0.05, respectively), duration of meth use and experience of opioid use were significantly associated with poor attention (p < 0.05), and processing speed (p < 0.05). We also found that earlier age of first meth use was significantly associated with poor verbal memory (p < 0.05). Amount of meth consumption was also found to be significantly associated with deficit in motor speed (p < 0.05). Conclusion: Duration of meth use and experience of ketamine use predicted cognitive deficits in meth users in this study. The mechanisms behind association of various meth use parameters with deficits in different domains of cognition warrant further investigation.

Key words: methamphetamine, cognition, ketamine, substance abuse

Introduction

Methamphetamine (meth) is a potent central nervous system stimulant with high addiction potential. Addiction to meth remains a major public health problem in the world, and has caused significant medical, psychiatric, and behavioral consequences. Comparing to other neurotoxic substances, meth may be more potent because of its high lipid-solubility and rapid diffusion across of the blood-brain-barrier [1, 2]. Meth associated central nervous system effects can involve in a various metabolic, structural, and functional brain changes which may have an effect on cognitive function. Long-term effects of meth may be especially problematic in frontostriatal circuits, where potential consequences include neural injury in the striatum and prefrontal cortex [1, 3]. Functional alteration and impairment may persist for a long time even after meth use is discontinued.

Numerous factors can affect the extent of the impact of meth use on cognition. A meta-analysis [4] showed that neurocognitive effects of meth may potentially be explained by factors, including demographic (age, gender, education level, etc.) and meth use parameters. Some studies have reported that the rates of cognitive impairment are correlated with frequency [5] or amount of meth use [6], while others show that no association of cognitive function exists using measures of the severity of meth dependence or the frequency, amount or the duration of use [7-10]. In addition, use of other substance also affects cognitive functioning, particularly since many meth users are also extensive poly-drug users, with high levels of opioid, other stimulant and ketamine use. Although the actual impacts of characteristic factors on cognitive performance meth users remain unknown, the cognitive difference between meth users and healthy control subjects might be in fact driven by these variables. Therefore, the objective of this study was to study what meth use parameters can predict cognitive deficits in meth users.

Methods

Study participants

The study protocol was approved by the Chang Gung Memorial Hospital institutional review board, with the need to obtain informed consents from the study participants. This study is cross-sectional in design. The inclusion criteria for meth users into this study were (A) meth abuse or meth dependence was defined using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) [11]; and (B) patients’ age were greater or equal to 18 years. Excluded from the study were (A) patients with a history of psychosis before meth use, (B) those whose psychosis was clearly associated to the abuse of other psychedelic drugs, (C) and those who were opportunistic (being less than 20 times during a one-year period) meth users.

Ultimately, 131 meth users were enrolled in this study from: (A) a detention center in New Taipei City, Taiwan; (B) a general hospital (Keelung Chang Gung Memorial Hospital); and (C) two psychiatric hospitals (the Taipei City Hospital, Song-De Branch and the Yu-Li Psychiatric Center). The meth users in the detention center were required to wait in an examination room so that their addiction severity was evaluated. Those participants were assured that their legal status would not be affected by whether they provided information and that all personal information would be kept confidential. The other meth users were found and enrolled in the outpatient clinics or on the psychiatric wards. The researchers interviewed the patients and did neu-
ropsychological tests when they had not used meth for at least one week with a negative test on a urine drug screen, and while their psychotic symptoms were relatively stable, at least one week after admission if admitted was due to acute psychosis.

**Diagnostic assessment**

Once informed consent was obtained from the participants, they were interviewed using the Diagnostic Interview for Genetic Studies (Chinese version) (DIGS-C) [12], which contains a detailed evaluation of the longitudinal course of illness, emphasizing the comorbidities of substance abuse [13]. A senior psychiatrist reviewed the medical record of each DIGS-C interview and then diagnosed the participants with a meth-related disorder or a psychiatric disorder in accordance with DSM-IV-TR criteria [11]. A satisfactory inter-rater reliability score for this research (κ for meth psychosis was 0.92) was determined using a previously described method [14].

**Neurocognitive evaluation**

The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate the neurocognitive functions of all participants [15]. The BACS is an instrument to evaluate the elements of cognition that are most commonly impaired and strongly connected with real-world functioning aspects in patients with schizophrenia [16]. The BACS evaluation takes roughly 30 minutes, yielding a high completion rate in patients, with a high test-retest reliability. The BACS evaluation includes the list-learning test, digit-sequencing task, token-motor task, category-instances test, controlled-oral-word-association test, symbol coding, and Tower of London test, to measure verbal memory, working memory, motor speed, verbal fluency, attention, processing speed, and executive function, respectively. The primary measure of each BACS domain is standardised by creating T- or Z-scores, and a composite score is calculated by comparing a patient’s performance of each measure to the performance of the subjects of the healthy control group. For the primary measure of each BACS domain standardised by creating Z-scores, the composite score is the Z-score of that sum [17]. Meanwhile, a T-score of 50 indicates average functioning in reference to the healthy population with the same age and gender; every 10 points represents one standard deviation. This study used T-scores for each scale for analysis.

**Demographic characteristics and patterns of meth use**

All participants were personally interviewed using a structured questionnaire to collect information on their socio-demographic characteristics (i.e. gender, age, marital status, education levels, and employment status), and their history of antipsychotic medications. Furthermore, we did chart reviews to confirm the drug class and dosage of the antipsychotic drugs that the study participants were then using. We also converted daily doses of antipsychotic drugs according to the daily dose suggested by the World Health Organization, Collaborating Centre for Drug Statistics Methodology (www.whocc.no/ate_ddi_index/2012). The meth users were further questioned on their patterns of drug use, including illicit drug use apart from meth, their age of first meth use, total duration of meth use, and duration of meth abstinence.

**Psychopathological evaluation**

The Brief Psychiatric Rating Scale (BPRS) was used in this study to evaluate the clinical psychopathology of all study participants. The 18-
item BPRS has been widely applied in both clinical and pharmaceutical research to measure general psychopathology, and is valid for both patients with psychosis and meth users [18]. A 7-point Likert-scale, with higher scores indicating greater severity, was used to rate all of the items. Subscale scores were calculated using small sets of variables based on the three domains of the Positive and Negative Syndrome Scale (PANSS) – positive, negative, and general psychopathological symptoms [19].

**Statistical analysis**

In this study, categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate, whereas one-way analysis of variance was used to compare continuous variables among all groups. We used multivariate analysis of covariance (MANCOVA) as the principal analytic strategy to determine intergroup differences in the BACS performance. The T-scores from the six domains mentioned above and the composite score of BACS were used as the dependent variables. We used age, sex, and level of education as covariates in the MANCOVA model in an effort to control any confounding effects. We applied Bonferroni-corrected *post hoc* tests in an attempt to reduce type I errors in the MANCOVA model.

The Statistical Package for Social Science software version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used to analyse the data results, and variables were presented as either mean (± standard deviation), or frequency (%). In a two-tailed test, *p < 0.05* was considered statistically significant.

**Results**

Totally, we recruited 131 patients with meth use. Table 1 lists demographic characteristics, patterns of substance use, psychopathology and neurocognitive functions of meth users (N = 131). Table 2 describes effects of age, sex, level of education, and patterns of substance use on each BACS domain in patients with the meth use (N = 131).

**Discussion**

In this study (Table 2), we found that longer duration of meth use was significantly associated with poor attention and processing speed (*p < 0.05*), working memory (*p < 0.01*), executive function (*p < 0.05*), and global cognitive performance (*p < 0.01*). Experience of ketamine use in meth users (Table 2) was also found to be significantly associated with poor working memory (*p < 0.01*), executive function (*p < 0.05*), and global composite score (*p < 0.05*).

Many studies have shown relationships between duration of meth use and extent of dopaminergic dysfunction [20, 21]. A database collected in laboratory animal also suggested that long-term administration of meth produces disruptive effects in several cognitive domains [22]. Researches using other measures of meth administration such as frequency of use or amount of recent use have also demonstrated similar results [6, 23]. But associations between duration of meth use and cognitive function in meth users still remain inconclusive. Some studies have not shown the relationship between cognition and estimates of cumulative lifetime dose [7, 8, 24], whereas several studies have not been found relationship between cognitive performance and duration of meth use [22, 24]. A possible explanation for this inconsistent finding is due to different subject compositions between studies. Some studies have assessed cognition of abstinent meth users while others have assessed acute effect of meth use.
Table 1. Demographic characteristics, patterns of substance use, psychopathology and neurocognitive functions of the methamphetamine (meth) users (N = 131)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.5 ± 8.0</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>27 (20.6)</td>
</tr>
<tr>
<td>Men</td>
<td>104 (79.4)</td>
</tr>
<tr>
<td>Marital status(^a), n (%)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>26 (19.8)</td>
</tr>
<tr>
<td>Single</td>
<td>39 (29.8)</td>
</tr>
<tr>
<td>Divorced or separated or widowed</td>
<td>62 (47.3)</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>77 (58.8)</td>
</tr>
<tr>
<td>Level of education (years)</td>
<td>9.4 ± 2.0</td>
</tr>
<tr>
<td>Age at first meth use (years)</td>
<td>20.8 ± 6.1</td>
</tr>
<tr>
<td>Duration of meth use (months)</td>
<td>27.6 ± 41.6</td>
</tr>
<tr>
<td>Dose of meth per week (g)</td>
<td>4.3 ± 4.5</td>
</tr>
<tr>
<td>Duration of meth abstinence (weeks)</td>
<td>172.3 ± 299.7</td>
</tr>
<tr>
<td>Experience of other illicit drug use, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>24 (18.3)</td>
</tr>
<tr>
<td>MDMA</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>Opioid</td>
<td>35 (26.7)</td>
</tr>
<tr>
<td>Current antipsychotic drugs, n (%)</td>
<td>43 (32.8)</td>
</tr>
<tr>
<td>Psychopathology(^b)</td>
<td></td>
</tr>
<tr>
<td>BPRS total score</td>
<td>30.4 ± 10.9</td>
</tr>
<tr>
<td>BPRS positive symptoms</td>
<td>13.3 ± 6.0</td>
</tr>
<tr>
<td>BPRS negative symptoms</td>
<td>7.5 ± 3.2</td>
</tr>
<tr>
<td>BPRS general symptoms</td>
<td>9.6 ± 3.7</td>
</tr>
<tr>
<td>Neurocognitive assessment (BACS) (T-score)</td>
<td></td>
</tr>
<tr>
<td>Verbal memory</td>
<td>31.2 ± 11.3</td>
</tr>
<tr>
<td>Working memory</td>
<td>45.5 ± 12.5</td>
</tr>
<tr>
<td>Motor speed</td>
<td>45.8 ± 12.5</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>24.5 ± 5.9</td>
</tr>
<tr>
<td>Attention and processing speed</td>
<td>35.5 ± 12.1</td>
</tr>
<tr>
<td>Executive function</td>
<td>41.7 ± 16.7</td>
</tr>
<tr>
<td>Composite score</td>
<td>29.8 ± 14.3</td>
</tr>
</tbody>
</table>

BACS, the Brief Assessment of Cognition in Schizophrenia; BPRS, the Brief Psychiatric Rating Scale; MDMA, 3,4-methylenedioxy-methamphetamine.

\(^a\) Four patients has missing data

\(^b\) Only meth users with experience of psychotic symptoms (n = 100) were assessed by the BPRS
Whether the subjects are psychotic also matters. Our previous study revealed that persistent psychosis indicates cognitive decline in meth users [25].

Our finding (Table 2) showed that overall cognitive performance and some BACS domains were significantly associated with duration of meth use. The significant association in our study may enhance the assumption that some specific cognitive function or even global cognitive function would be disrupted following prolonged meth doses administered repeatedly, and that longer duration meth use might lead to accumulative neurotoxic effect to human cognition. Therefore, we suggest that longer duration of meth use might be a predictor in cognitive deficit in meth users.

Based on our findings (Table 2), we suggest that concomitant use of other substances with meth may involve different domains of cognitive function. Our finding implicates that N-methyl-D-aspartate (NMDA) glutamate receptors and dopamine systems conjointly may contribute to more severe cognitive deficit. The pattern of the interactive effects of ketamine and meth is consistent with the hypothesis that facilitation of prefrontal cortical dopamine levels would attenuate some cognitive impairment associated with deficits in NMDA receptor function. Previous studies have shown that ketamine may disrupt dopaminergic neurotransmission, and cognitive function, possibly by stimulating postsynaptic non-NMDA glutamate receptors [26]. In an adult mouse brain, conjunctive use ketamine can potentiate meth-induced dopamine neurotoxicity through AMPA/kainite activation, and that conjunctive use of methamphetamine can aggravate ketamine-induced glutamatergic neurotoxicity possibly through D1 receptor activation [27]. Concomitant exposure to meth and ket-

![](http://example.com/table)
amine warrants particular attention since both these two kinds of substance are popularly abused in Taiwan and lead to severe physical and mental consequences [28, 29].

The results of our study (Table 2) also showed that higher dose of meth consumption was significantly associated with poor motor speed ($p < 0.05$). This finding is in line with a previous study that greater average meth consumes in the previous 12 months is associated with motor impairment [24], and the findings from an animal study that binge use tends to cause brain injury [30]. Our results here are compatible with previous studies demonstrating that meth-induced neurotoxicity is associated with fine motor skills [21, 31]. Although many early preclinical studies have reported pronounced motor effects from high dose of meth use, but the prevalence of severe movement abnormality in both clinical practice and in the literatures has been less than what might be expected given the striatum to meth associated neurotoxicity [32]. It is possible that some domains of cognitive function are more likely to be disrupted at certain life stages. For example, exposure to substances in childhood or adolescence may produce long-lasting changes in cognition [33]. In our study (Table 2), we found that earlier first meth use was significantly associated with poor verbal memory ($p < 0.05$). But a previous study has not shown the association between younger age at first use and poor cognitive function [34].

**Study limitations**

The readers are warned not to over-interpret this study results because the study has three limitations:

- The sample size in this study is not big enough to detect small differences in cognitive function between groups.
- Some participants’ clinical characteristics such as smoking and drinking behavior, routes of substance use, previous treatment, comorbid illnesses (such as personality disorders), attention deficit-hyperactivity disorder, infectious disease were not collected in this study.
- Information on drug use patterns were self-reported in this study and might be affected by respondents’ ability to recall.

Apparently, future studies with the designs to address the above-listed three limitations, are needed to validate the study data.

**Summary**

 Longer duration of meth use and the experience of ketamine use might denote risks on cognitive deficits in meth users in this study. Other meth use parameters may influence certain domains of cognitive function. The mechanisms behind association of various meth use parameters with deficits in different domains of cognition warrant further investigation.

**Acknowledgments**

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